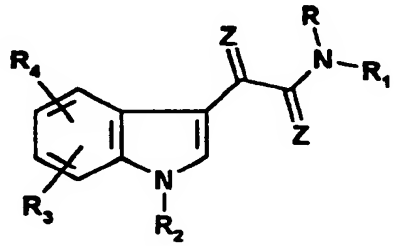
Patent Claims

1. Use of N-substituted indole-3-gloxylamides [sic] of the general formula 1 as antitumor agents according to Main Patent Application 19 814 838.0 for tumor treatment in particular in the case of pharmaceutical resistance and metastasizing carcinoma, and also as angiogenesis inhibitors, with markedly lower side effects in particular markedly lower neurotoxicity



Formula 1

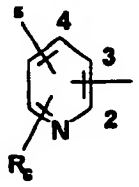
where the radicals R, R_1, R_2, R_3, R_4 and Z have the following meaning:

R is hydrogen, (C_1-C_6)-alkyl, where the alkyl group can be mono- or polysubstituted by the phenyl ring and this phenyl ring for its part can be mono- or polysubstituted by halogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, by carboxyl groups, carboxyl groups esterified with C_1-C_6-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups, benzyloxy groups and by a benzyl group which is mono- or polysubstituted in the phenyl moiety by (C_1-C_6)-alkyl groups, halogen atoms or trifluoromethyl groups,

R is further the benzyloxycarbonyl group (Z group) and the tertiary-butoxycarbonyl radical (BOC radical), furthermore the acetyl group.

R_1 can be the phenyl ring, which is mono- or polysubstituted by (C_1-C_6)-alkyl, (C_1-C_6)-

alkoxy, cyano, halogen, trifluoromethyl, hydroxyl, benzyloxy, nitro, amino, (C_1-C_6)-alkylamino, (C_1-C_6)-alkoxycarbonylamino and by the carboxyl group or by the carboxyl group esterified with C_1-C_6-alkanols, or can be a pyridine structure of the formula 2 and its N-oxide [sic]



Formula 2

and its N-oxide, where the pyridine structure is alternatively bonded to the ring carbon atoms 2, 3 and 4 and can be substituted by the substituents R_5 and R_6. The radicals R_5 and R_6 can be identical or different and have the meaning (C_1-C_6)-alkyl and the meaning (C_3-C_7)-cycloalkyl, (C_1-C_6)-alkoxy, nitro, amino, hydroxyl, halogen and trifluoromethyl and further are the ethoxycarbonylamino radical and the group carboxyalkyloxy in which the alkyl group can have 1-4 C atoms.

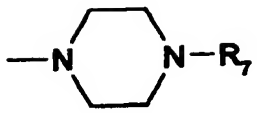
R_1 can further be a 2- or 4-pyrimidinyl heterocycle, where the 2-pyrimidinyl ring can be mono- or polysubstituted by the methyl group, furthermore are [sic] the 2-, 3-, and 4- and 8-quinolyl structure substituted by (C_1-C_6)-alkyl, halogen, the nitro group, the amino group and the (C_1-C_6)-alkylamino radical, are [sic] a 2-, 3- and [sic] 4-quinolylmethyl group, where the ring carbons of the pyridylmethyl radical of the quinolyl group and of the quinolylmethyl radical can be substituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, nitro, amino and (C_1-C_6)-alkoxycarbonylamino.

R_1, in the case in which R = hydrogen, the methyl or benzyl group and the benzyloxycarbonyl radical (Z radical), the tert-butoxycarbonyl radical (BOC radical) and the acetyl group, can furthermore be the following radicals: $-CH_2COOH$; $-CH(CH_3)-COOH$; $-(CH_3)_2-CH-(CH_2)_2-CH-COO-$; $H_3C-H_2C-CH(CH_3)-CH(COOH)-$ [sic]; $HO-H_2C-CH(COOH)-$; phenyl-CH_2-$CH(COOH)-$; (4-imidazolyl)-CH_2-$CH-(COOH)-$; $HN=C(NH_2)-NH-(CH_2)_3-CH(COOH)-$; $H_2N-(CH_2)_4-CH(COOH)-$; $H_2N-CO-CH_2-CH-(COOH)-$; $HOOC-(CH_2)_2-CH(COOH)-$;

R_1, in the case in which R is hydrogen, the Z group, the BOC radical, the acetyl or the benzyl group, can furthermore be the acid radical of a natural or unnatural amino acid, e.g. the α-glycyl, the α-sarcosyl, the α-alanyl, the α-leucyl, the α-isoleucyl, the α-seryl, the α-phenylalanyl, the α-histidyl, the α-prolyl, the α-arginyl, the α-lysyl, the α-asparagyl and the α-glutamyl radical, where the amino groups of the respective amino acids can be present unprotected or can be protected. A possible protective group of the amino function is the carbobenzoxy radical (Z radical) and the tert-butoxycarbonyl radical (BOC radical) as well as the acetyl group. In the case of the asparagyl and glutamyl radical claimed for R_1, the second, unbonded carboxyl group is present as a free carboxyl group or in the form of an ester with C_1-C_6-alkanols, e.g. as a methyl, ethyl or as a tert-butyl ester.

Furthermore, R_1 can be the allylamino-carbonyl-2-methylprop-1-yl group.

R and R_1 can further form, together with the nitrogen atom to which they are bonded, a piperazine ring of the formula 3 or a homopiperazine ring, provided R_1 is an aminoalkylene group, in which



Formula 3

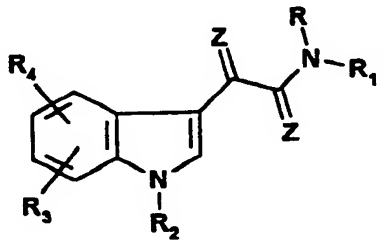
R_7 is an alkyl radical, is a phenyl ring which can be mono- or polysubstituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, halogen, the nitro group, the amino function and by the (C_1-C_6)-alkylamino group. R_7 is furthermore the benzhydryl group and the bis-p-fluorobenzylhydryl group [sic].

R_2 can be hydrogen and the (C_1-C_6)-alkyl group, where the alkyl group is mono- or polysubstituted by halogen and phenyl, which for its part can be mono- or polysubstituted by halogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl groups, carboxyl groups esterified with C_1-C_6-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups or benzyloxy groups. The (C_1-C_6)-alkyl group counting as R_2 can further be substituted by the 2-quinolyl group and the 2-, 3- and 4-pyridyl structure, which can both in each case be mono- or polysubstituted by halogen, (C_1-C_4)-alkyl groups or (C_1-C_4)-alkoxy groups. R_2 is further the aroyl radical, where the aryl moiety on which this radical is based is the phenyl ring, which can be mono- or polysubstituted by halogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl groups, carboxyl groups esterified with C_1-C_6-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups or benzyloxy groups.

R_3 and R_4 can be identical or different and are hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_1-C_6)-alkanoyl, (C_1-C_6)-alkoxy, halogen and benzyloxy. R_3 and R_4 can furthermore be the nitro group, the amino group, the (C_1-C_4)-mono or dialkyl-substituted amino group, and the (C_1-C_6)-alkoxycarbonylamino function or (C_1-C_6)-alkoxycarbonylamino-(C_1-C_6)-alkyl function.

Z is O and S.

2. Use of N-substituted indole-3-gloxylamides [sic] according to claim 1 general formula 1a for tumor treatment in particular in the case of pharmaceutical resistance and metastasizing carcinoma, and also as angiogenesis inhibitors, with markedly lower side effects in particular markedly lower neurotoxicity



Formula 1 a

where the radicals

R = hydrogen

R_1 = 4-pyridyl, 4-fluorophenyl

R_2 = benzyl, 4-chlorobenzyl, 4-fluorobenzyl, 3-pyridylmethyl, 4-bromobenzyl

R_3 and R_4 = hydrogen and

Z is oxygen.

3. Pharmaceutical composition for tumor treatment in particular in the case of pharmaceutical resistance and metastasizing carcinoma, and also as angiogenesis inhibitors, with markedly lower

side effects in particular markedly lower neurotoxicity characterized, in that it contains at least one of the compounds of the general formula 1 or 1a, optionally also they [sic] as acid addition salts, for example as salts of mineral acids, such as hydrochloric acid, sulfuric acid, phosphoric acid, salts of organic acids, such as, for example, acetic acid, lactic acid, malonic acid, maleic acid, fumaric acid, gluconic acid, glucuronic acid, citric acid, embonic acid, methanesulfonic acid, trifluoroacetic acid, succinic acid and 2-hydrop0xyethanesulfonic acid [sic] and possibly their N-oxides.

4. Use of N-substituted indole-3-glyoxylamides of the general formula 1 or 1a and their physiologically tolerable acid addition salts for the production of antitumor agents for use in particular in the case of pharmaceutical resistance and metastasizing carcinoma, and also as angiogenesis inhibitors, with markedly lower side effects in particular markedly lower neurotoxicity namely in particular the following compounds or their salts with physiologically tolerable acids or if possible their N-oxides:

D 24241 N-(pyridin-4-yl)-[1-(4-fluorobenzyl)-indole-3-yl]glyoxylamide

D 24843 N-(pyridin-4-yl)-(1-benzylindole-3-yl)-glyoxylamide

D 24850 N-(4-fluorophenyl)-[1-(3-pyridylmethyl)-indole-3-yl]glyoxylamide

D 24851 N-(pyridin-4-yl)-[1-(4-chlorobenzyl)-indole-3-yl]glyoxylamide

D 25505 N-(pyridin-4-yl)-[1-(4-fluorobenzyl)-indole-3-yl]glyoxylamide HCL [sic]

5. Antitumor agents comprising as active agent one or more N-substituted indole-3-gloxylamides according

to the general formula 1 or 1a and optionally their physiologically tolerable acid addition salts, for use in particular in the case of pharmaceutical resistance and metastasizing carcinoma, and also as angiogenesis inhibitors, with markedly lower side effects in particular markedly lower neurotoxicity but in particular one or more compounds according to claim 4.

6. Antitumor agents for tumor treatment in particular in the case of pharmaceutical resistance and metastasizing carcinoma, and also as angiogenesis inhibitors, with lower side effects in particular markedly lower neurotoxicity comprising as active agent namely in particular

D 24241 N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-indole-3-yl]glyoxylamide or its hydrochloride

7. Antitumor agents for tumor treatment in particular in the case of pharmaceutical resistance and metastasizing carcinoma, and also as angiogenesis inhibitors, with markedly lower side effects in particular markedly lower neurotoxicity comprising as active agent namely in particular

D 24843 N-(Pyridin-4-yl)-(1-benzylindole-3-yl) glyoxylamide.

8. Antitumor agents for tumor treatment in particular in the case of pharmaceutical resistance and metastasizing carcinoma, and also as angiogenesis inhibitors, with markedly lower side effects in particular markedly lower neurotoxicity comprising as active agent and namely in particular

D 24850 N-(4-Fluorophenyl)-[1-(3-pyridylmethyl)-indole-3-yl]glyoxylamide

9. Antitumor agents for tumor treatment in particular in the case of pharmaceutical resistance and

metastasizing carcinoma, and also as angiogenesis inhibitors, with markedly lower side effects in particular markedly lower neurotoxicity comprising as active agent and namely in particular comprising as active agent comprising as active agent

D 24851 N-(Pyridin-4-yl)-[1-(4-chlorobenzyl)-indole-3-yl]glyoxylamide

10. Antitumor agent for tumor treatment in particular in the case of pharmaceutical resistance and metastasizing carcinoma, and also as angiogenesis inhibitors, with markedly lower side effects in particular markedly lower neurotoxicity comprising as active agent comprising as active agent one or more N-substituted indole-3-gloxylamides according to the general formula 1 or 1a and optionally their physiologically tolerable acid addition salts and, if possible, N-oxides, but in particular one or more compounds according to claim 4 and 6 to 8 and a pharmaceutically utilizable excipient and/or diluent or auxiliary in the form of tablets, coated tablets, capsules, solutions for infusion or ampoules, suppositories, patches, powder preparations which can be employed by inhalation, suspensions, creams and ointments.

11. Use of N-substituted indole-3-glyoxylamides of the general formula 1 or 1a and their physiologically tolerable acid addition salts as angiogenesis inhibitors namely in particular of the following compounds or their salts with physiologically tolerable acids or if possible their N-oxides:

D 24241 N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-indole-3-yl]glyoxylamide

D 24843 N-(Pyridin-4-yl)-(1-benzylindole-3-yl)-glyoxylamide

D 24850 N-(4-Fluorophenyl)-[1-(3-pyridylmethyl)-indole-3-yl]glyoxylamide

D 24851 N-(Pyridin-4-yl)-[1-(4-chlorobenzyl)-indole-3-yl]glyoxylamide

D 25505 N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-indole-3-yl]glyoxylamide HCL [sic]

12. Use of N-substituted indole-3-glyoxylamides of the general formula 1 or 1a and their physiologically tolerable acid addition salts for use in particular in the case of pharmaceutical resistance and as a replacement for antitumor agents which are no longer effective on account of resistance formation in particular of the compounds

D 24241 N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-indole-3-yl]glyoxylamide

D 24843 N-(Pyridin-4-yl)-(1-benzylindole-3-yl)-glyoxylamide

D 24850 N-(4-Fluorophenyl)-[1-(3-pyridylmethyl)-indole-3-yl]glyoxylamide

D 24851 N-(Pyridin-4-yl)-[1-(4-chlorobenzyl)-indole-3-yl]glyoxylamide

D 25505 N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-indole-3-yl]glyoxylamide HCL [sic]

13. Use of N-substituted indole-3-glyoxylamides of the general formula 1 or 1a and their physiologically tolerable acid addition salts for use in particular in the case of pharmaceutical resistance in fixed or free combination with known antitumor agents and as a replacement for antitumor agents which are no longer active on account of resistance formation in particular of the compounds

D 24241 N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-indole-3-yl]glyoxylamide

D 24843	N-(Pyridin-4-yl)-(1-benzylindole-3-yl)-glyoxylamide
D 24850	N-(4-Fluorophenyl)-[1-(3-pyridylmethyl)-indole-3-yl]glyoxylamide
D 24851	N-(Pyridin-4-yl)-[1-(4-chlorobenzyl)-indole-3-yl]glyoxylamide
D 25505	N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-indole-3-yl]glyoxylamide HCL [sic]